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EXAMINER	
MYERS, CARLA J	
ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
11/17/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/517,741	FOEKENS ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 November 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,20-22,24,45,57-59,61,62,67 and 77* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 20-22, 24, 45, 57-59, 61, 62, 67 and 77* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the amendment filed on November 3, 2010. Applicant's arguments and amendments to the claims presented in the reply of November 3, 2010 have been fully considered but are not persuasive to place all claims in condition for allowance. All rejections not reiterated herein are hereby withdrawn. In particular, the rejection of claims 1, 20-22, 24, 45, 57-59, 61, 62, 67 and 77 under 35 U.S.C. 112, second paragraph has been obviated by the amendments to the claims.

2. Claims 1, 20-22, 24, 45, 57-59, 61, 62, 67 and 77 are pending and have been examined herein.

3. The following rejections were previously applied in the Office action of May 3, 2010 and have been modified herein to address Applicant's amendments to the claims.

Claim Rejections - 35 USC § 112, first paragraph - Enablement

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 20-22, 24, 45, 57-59, 61, 62, 67 and 77 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for determining if a human subject having an estrogen receptor-positive breast cancer has a high risk of relapse or a low risk of relapse following adjuvant tamoxifen treatment comprising obtaining from a human subject having estrogen receptor-positive breast cancer a biological sample comprising breast cancer cell genomic DNA, amplifying PITX2 genomic DNA present in said biological sample using the primers of SEQ ID

NO: 1055 and 1056 to obtain amplified PITX2 nucleic acids, analyzing the amplified PITX2 nucleic acids to determine their methylation status, and determining that the human subject has a low risk of relapse following adjuvant tamoxifen treatment if the amplified PITX2 nucleic acids are hypomethylated as compared to the methylation status of a control and that the human subject has a high risk of relapse following adjuvant tamoxifen treatment if the amplified PITX2 nucleic acids are hypermethylated compared to the methylation status of a control,

does not reasonably provide enablement for methods which determine if a human subject having an estrogen receptor-positive breast cancer has a high or low risk of relapse following any adjuvant therapeutic treatment that inhibits an estrogen receptor pathway, methods which analyze any genomic DNA from a subject to determine it's methylation status, methods which analyze a single CpG of SEQ ID NO: 83 and methods which analyze the methylation status of any contiguous portion (i.e., 2 nucleotides etc) to ascertain the methylation status of the PITX2 gene as indicative of a high or low relapse following adjuvant therapy. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

This rejection was previously presented in the Office action of May 3, 2010 and is maintained for the reasons set forth therein.

Response to Remarks:

It is first noted that those aspects of the prior rejection as they pertained to methods for predicting any response to an adjuvant therapy have been obviated by the

amendment to the claims to recite a method "for determining if a human subject having an estrogen receptor-positive breast cancer has a high risk of relapse or a low risk of relapse following adjuvant therapeutic treatment" wherein a determination of "hypomethylation of SEQ ID NO: 83, complements thereof, and contiguous portions thereof is indicative of low risk for relapse following adjuvant therapeutic treatment and hypermethylation of SEQ ID NO: 83, complements thereof, and contiguous portions thereof is indicative of high risk for relapse following adjuvant therapeutic treatment." Further, in view of Applicant's amendments to the claims and clarification of the teachings in the specification, the claims are considered to be enabled for the subject matter set forth above. It is also noted that at pages 10-11 of the response, it is stated that "Applicants confirm that oligonucleotide number 3522:2087 refers to detection oligonucleotide SEQ ID NOS:2027 and 2028, which were disclosed in the originally filed Sequence Listing."

Regarding those aspects of the rejection as they pertain to the analysis of any biological sample from a human subject to determine the methylation status of SEQ ID NO: 83 as indicative of risk of relapse following adjuvant therapy, the response states that the claims have been amended to clarify that the biological sample comprises genomic DNA of breast cancer cells. However, while claims 1, 20-22 and 24 recite a step of obtaining a sample comprising breast cancer cell genomic DNA, the claims do not require that the breast cancer cell genomic DNA is analyzed to determine its methylation status. Rather, the claims broadly recite a step of "determining the genomic DNA methylation status of at least one CpG dinucleotide of at least one target nucleic

acid sequence of the PITX2 gene." The claims do not recite a nexus between the obtaining a sample step and the determining the methylation status step. Thereby, the claims as broadly written still encompass determining the methylation status of SEQ ID NO: 83 in any biological sample (skin, blood, serum, saliva etc) obtained from a human subject.

Further, particularly with respect to claim 77, it is maintained that is unpredictable as to whether the methylation status of a biological sample that is a cell line derived from a subject can be analyzed for its methylation status as indicative of risk of relapse. As set forth in the rejection, it is well accepted that the genetic alterations which occur in cell lines are not necessarily reflective of the genetic changes which occur *in vivo*. Dermer was cited for its teachings that "The cell lines in which cancer is usually studied are unsuitable for the job. They do not mimic conditions in the human body." Dermer concludes that "Petri dish cancer is really a poor representation of malignancy, with characteristics profoundly different from the human disease." Since the results obtained in vitro in cell lines cannot be extrapolated to in vivo, knowledge that a gene is methylated or not methylated in a cell line does not allow one to conclude that this gene is associated with response to treatment *in vivo*. The response does not specifically address this aspect of the rejection.

The response states that:

"According to Example 1 data set 1 p40 primers 1055 and 1056 are used for amplifying the PITX2 amplificate which is then hybridized to the PITX2 detection oligos of Table 2 (see "Bisulfite treatment and mPCR" and "Hybridisation"). Thus the oligos of Table 2 (2023-2028) explicitly define all the CpG positions of the amplificate. From comparing the sequence of the oligos it becomes clear that:

(a) they form 3 pairs: 2023+2024; 2025+2026; 2027+2028;

(b) each oligo covers 2 CpG positions
(c) oligos 2023, 2025, and 2027 detect the methylated Cs, respectively; and
(d) oligos 2024, 2026, and 2028 detect the un-methylated Cs, respectively

Applicants further point out the specification teaches that the amplicon and these CpG positions are within a CpG island wherein co-methylation would be reasonably be expected, and is thus inherent in the design of the detection oligos as both CpG positions within each oligo art designed to detect coordinate methylation, and so effective hybridization of any given oligo would not be possible absent co-methylation. Therefore, the methylation data of Figures 5 and 6 inherently corroborate that co-methylation is occurring within the amplicon, and in this sense one of skill in the art would understand that the specification teaches at least that any CpG of the detection oligos can be used, and that this would reasonably be expected to extend across the amplicon of the CpG island. Applicants further point out that given the explicit disclosure of exemplary CpG positions (e.g., within the PITX2 detection oligos and amplicon), one of ordinary skill in the art could readily determine without undue effort (i.e., within a few days or a week, given array-based methods available at the time of filing) whether any other particular CpG position within the claimed PITX2 sequence was coordinately methylated with CpGs of the explicitly disclosed detection oligos, and therefore readily practice the invention commensurate with the claimed scope."

These arguments have been fully considered but are not persuasive. As acknowledged in the response, all data provided in the specification was obtained by analyzing a fragment of SEQ ID NO: 83 – i.e., the fragment of 408bp obtained using the primers of SEQ ID NO: 1056 and 1055. As indicated in the arguments above, 6 CpGs in this 408bp region were analyzed for their methylation status to determine an association between methylation status and risk of relapse following adjuvant treatment with tamoxifen. This is in contrast to the present claims which recite analyzing any single CpG at any location within the 6,343 bp of SEQ ID NO: 83. That specification has not established that a single CpG alone can be used to reasonably predict risk of relapse following tamoxifen adjuvant treatment. Nor has the specification established that regions outside of the 408bp region – i.e., any of the other 5,935 bases of SEQ ID NO: 83 consist of a CpG that is hypomethylated or hypermethylated in subjects showing a

low or high risk of relapse following tamoxifen adjuvant treatment. The unpredictability of analyzing a single CpG as indicative of a phenotype or of extrapolating the results obtained with one CpG to other CpG's is discussed in detail in the rejection of 5/3/10. In particular, the Office action cited Ushijima as teacgubg that "interpretation of differential methylation has proven difficult because the significance of methylation alterations depends on the genomic region, and functions of the CpG islands at specific sites have not been fully clarified" (see abstract). Ushijima teaches that both hypermethylation and hypomethylation are associated with the occurrence of cancer (page 223). Ushijima (page 223) also teaches that "it has become recognized that methylation in cancer cells frequently occurs in CGIs outside promoter regions, which do not repress gene transcription, and also in promoter CGIs of genes that cannot be regarded as tumour-suppressor genes. Even in normal cells, methylation of specific CGIs frequently occurs. Therefore, to identify novel tumour suppressor genes silenced in cancer cells by CGI methylation it is necessary to carefully select the particular CGIs to be included in the analysis." Accordingly, although Applicants assert that because methods are known in the art for determining methylation status of a nucleic acid and that such methods do not require undue experimentation to perform, such arguments are not persuasive because it is highly unpredictable as to which particular CpGs in particular regions of a genomic sequence will show an increase or decrease in their methylation status as indicative of a phenotype, such as risk of relapse following tamoxifen adjuvant therapy. The specification does not provide sufficient guidance as to how to identify additional CpGs in the 6,343 bp region of PITX2 (i.e., SEQ ID NO: 83) or how to use the

methylation status of a single CpG to predictive risk of relapse following adjuvant therapy.

At page 11, the response states that "with respect to the Examiner's contentions (pages 14-15) regarding the findings of Martens were discussed by Nimmrich et al. (Breast Cancer Research and Treatment. 2008. 111:429-437) (hereinafter "Nimmrich"), that Nimmrich refers to metastatic breast cancer and thus not to an adjuvant setting as presently claimed. Likewise, Martens refers to a metastatic setting (e.g. page 4101, left column, first paragraph and last paragraph, page 4102, right column, first paragraph). Applicants have amended the claims to recite application to the adjuvant setting."

However, while it is acknowledged that the Martens study analyzed patients treated with first line tamoxifen therapy, it is noted that the teachings of Martens were cited to establish the unpredictability in the art since the findings of Martens with first line tamoxifen therapy were the opposite of those of the present invention with adjuvant therapy. Again, Martens did not observe an association between methylation status of PITX2 and response to first line tamoxifen treatment in recurrent breast cancer (see Supplemental Tables 1 and 2). Martens (page 4101, col. 2) teaches that "(f)rom a biological point of view, however, first-line single agent endocrine therapy in patients with recurrent breast cancer is an excellent setting to study response to therapy because it is less subject to prognostic influences unavoidably present when a similar study would be done in the adjuvant setting." It is maintained that if the results obtained with Martens regarding response to tamoxifen in recurrent breast cancer are opposite those results purported by Applicants for adjuvant tamoxifen therapy, then this finding

supports the conclusion that it is unpredictable as to whether the results asserted in the specification could be extrapolated to any type of adjuvant therapy that inhibits any molecule or activity in an estrogen receptor pathway.

Also, it is again pointed out that in discussing the variation in results reported therein as compared to those of Widschwendter, Martens (page 4106, col. 1) states that the "reasons for the differences between that study and ours could be manifold including differences in study design (adjuvant versus first-line treatment), in the CpG sites analyzed, in the technology used, or in size or composition of the tissue collections used. Due to the heterogeneity of the cohorts and the likely confounding influence of steroid hormone receptor status, and different treatment modalities, the results of the study of Widschwendter et al are difficult to interpret." Thus, Martens teaches that while it is possible that there may be a difference in results between adjuvant therapy and first line therapy, it is equally possible that any differences in results may be due to a number of other factors including the identity of the CpG sites analyzed and the tissue sample analyzed. Martens notes that the absence of such information makes the results difficult to interpret. This is similar to the present situation wherein the claims encompass analyzing CpGs that are not within the region exemplified by the specification as showing hypomethylation or hypermethylation in subjects at risk of relapse following tamoxifen therapy.

The response asserts that undue experimentation would not be required to practice the claimed invention. It is argued that routine experimentation is permissible and that methods of high-throughput methylation assays could be used to determine the

methylation status within the PITX2 gene. Applicants conclude that they are entitled to claims that are commensurate in scope with that which one of skill in the art could obtain by virtue of what Applicants have disclosed.

These arguments have been fully considered but are not persuasive. Applicants arguments essentially indicate that it would be within the skill of the art to assay for methylation of PITX2 gene sequences. Applicants arguments do not establish that the results of performing such assays would be predictable and would allow the artisan to practice a method of predicting a risk of relapse following any adjuvant therapy that inhibits any molecule or activity in an estrogen receptor pathway in a breast cancer patient by determining the methylation status of any CpG in a PITX2 gene sequence of SEQ ID NO: 83 obtained from any tissue or fluid sample of an estrogen receptor positive breast cancer patient. While determining the methylation pattern of a gene is within the skill of the art, it is highly unpredictable as to the identity of particular methylation patterns that are associated with risk of relapse. The Office action establishes the unpredictability in the art of extrapolating the findings obtained with response to one type of adjuvant therapy to other types of adjuvant therapy, with the findings obtained with one tissue sample type to other tissue sample types and other cellular and acellular sample types, and with the results obtained regarding methylation status of one particular gene sequence (e.g., the 408bp promoter region of SEQ ID NO: 83 amplified using the primers of SEQ ID NO: 1056 and 1055) to other PITX2 gene sequences and particular CpG dinucleotides within other PITX2 gene sequences. Such

unpredictability is not overcome by the fact that methods are known in the art for determining the methylation status of a nucleic acid.

The response acknowledges that the data provided in the specification was obtained in subjects treated with tamoxifen adjuvant therapy. However, it appears that the response contends that the findings with tamoxifen therapy can be extrapolated to any adjuvant therapy that inhibits an estrogen receptor pathway because it is within the skill of the art to assay for methylation of SEQ ID NO: 83 without undue experimentation. Such arguments are not persuasive because it is maintained that the claims are not broadly drawn to methods for determining the methylation status of SEQ ID NO: 83, but rather the claims require predicting the risk of relapse in a subject following treatment with any adjuvant therapy. As stated on page 11 of the specification, the function of the PITX2 gene in the occurrence of cancer is currently unknown. As recently as 2008, Nimmrich states that "(f)rom a biological point of view, the role of PITX2 DNA-methylation and cancer is unknown" (page 435, col. 1). The lack of a clear structure – function relationship between PITX2 methylation and cancer, and particular response to treatment of cancer with drugs that target the estrogen receptor, further compounds the unpredictability of extrapolating results obtained with tamoxifen to other adjuvant therapies that inhibit an estrogen receptor pathway. In the absence of a showing in the specification of a correlation between a representative number of adjuvant therapies and hypermethylation or hypomethylation of one or more CpGs in SEQ ID NO: 83 and the absence of a clear-structure function relationship between hypermethylation or hypomethylation of one or more CpGs in SEQ ID NO: 83 and

response to adjuvant therapies that inhibit the estrogen receptor pathway, it is highly unpredictable as to whether the results obtained with tamoxifen adjuvant therapy can be extrapolated to other adjuvant therapies. Accordingly, in view of the unpredictability in the art, and the lack of disclosure in the specification and in the prior art and the unpredictability of the art, it is maintained that it would require undue experimentation for one of skill in the art to make and use the invention as broadly claimed.

Double Patenting

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 20-22, 24, 45, 57-59, 61, 62, 67, and 77 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3, 4, 6, 7, 11-13 and 16 of copending Application No. 10/582,705 in view of Berlin et al (WO 02/77272, 03 October 2002). Although the conflicting claims are not

identical, they are not patentably distinct from each. The present claims and the claims of '705 both comprise analyzing the methylation status of one or more CpGs in the PITX2 gene to predict a breast cancer subject's response to adjuvant therapeutic treatment. The present claims recite a method of determining if a subject has a high or low risk of relapse following adjuvant therapy, whereas the claims of '705 recite that the method is one that predicts the probability of response of a subject. However, when read in light of the specification, it is clear that subjects that do not respond to therapy are subjects at high risk of relapse. Further, the claims of '705 recite that the therapy is one that targets the estrogen receptor pathway and that the therapy is adjuvant therapy.

The claims of '705 do not specifically recite that the target sequence of the PITX2 gene comprises SEQ ID NO: 83. However, the claims of '705 do include analyzing the methylation status of the regulatory region in the PITX2 gene. Berlin et al disclose the promoter region of the PITX2 gene (SEQ ID NO: 47 therein) which consists of the same sequence as present SEQ ID NO: 83. Berlin teaches analyzing the methylation status of this PITX2 sequence to determine a correlation between the methylation status and the occurrence of hematopoietic cell proliferative disorders.

Since the claims of '705 encompass analyzing the methylation status of the regulatory region of CpG sequence in the PITX2 gene as indicative of response to adjuvant therapy in human breast cancer patients and because Berlin specifically teaches analysis of the methylation status of a PITX2 gene sequence, including the promoter region, which consists of a sequence identical to present SEQ ID NO: 83, it would have been obvious to one of ordinary skill in the art at the time the invention was

made to have modified the method claimed in '705 so as to have specifically analyzed the CpGs present in SEQ ID NO: 83 because methylation of these CpGs were known to occur in proliferative disorders and because the ordinary artisan would have recognized that the PITX2 gene sequence encompassed by the claims of '705 necessarily included the PITX2 promoter sequence of SEQ ID NO: 83 disclosed by Berlin et al.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Remarks:

In the response, it is stated that "Applicants have previously amended the claims to recite "complements thereof," in place of "sequences complementary thereto," such that the Examiner's underlying reliance on "complementarity" to SEQ ID NO:23 of '705 is not reasonably supported."

This argument is not persuasive because it does not pertain to the present grounds of rejection or the rejection as set forth on May 3, 2010. The rejection does NOT rely on a broad reading of "complementary" sequences.

The response states that "the pending application claims PITX2 as a treatment response predictive marker, whereas Applicants' Serial No. 10/582,705 ('078US0, P190US) claims PITX2 as prognostic marker, such that the two application claim distinct inventions."

This argument is not persuasive because it does not accurately characterize the claims of '705. The claims of '705 are not directed to "PITX2 as a prognostic marker." Rather, the claims of '705 recite a method for characterizing a cell proliferative disorder

of the breast tissues of a subject and determining characteristics of the proliferative disorder that include probability of response of a subject to one or more treatment regimens that target the estrogen receptor pathway, and particularly adjuvant treatment regimens. When considered in light of the specification of '705, predicting response to treatment includes predicting relapse following (adjuvant) treatment.

Lastly, the response states that the teaching of Berlin "relate to hematopoietic disorders, and thus does not support the Examiner's obviousness contention."

This argument has been fully considered but is not persuasive. Berlin has been cited because it teaches that the promoter (i.e., a regulatory) region of the PITX2 gene consists of a sequence that is identical to present SEQ ID NO: 83. Since the claims of '705 are inclusive of methods that analyze the regulatory region of the PITX2 gene and Berlin teaches that the promoter region (i.e., a regulatory region) of PITX2 consists of SEQ ID NO: 83, it is maintained that it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method claimed in '705 so as to have specifically analyzed the CpGs present in SEQ ID NO: 83 since SEQ ID NO: 83 constitutes the known promoter region of PITX2 and because methylation of these CpGs were known to occur in proliferative disorders.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is 571-272-0747. The examiner can normally be reached on Monday-Thursday (6:30-5:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Carla Myers/

Primary Examiner, Art Unit 1634